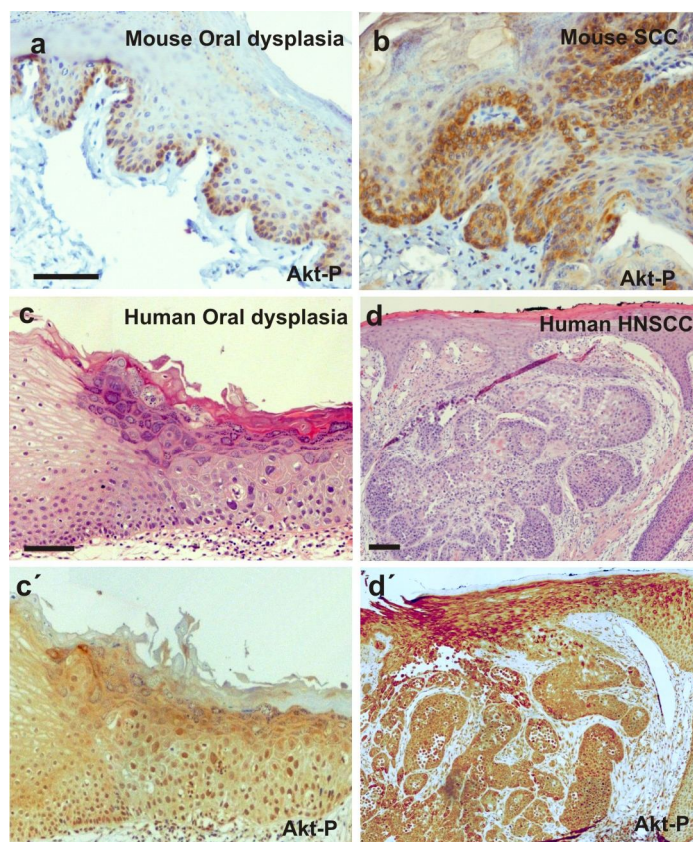
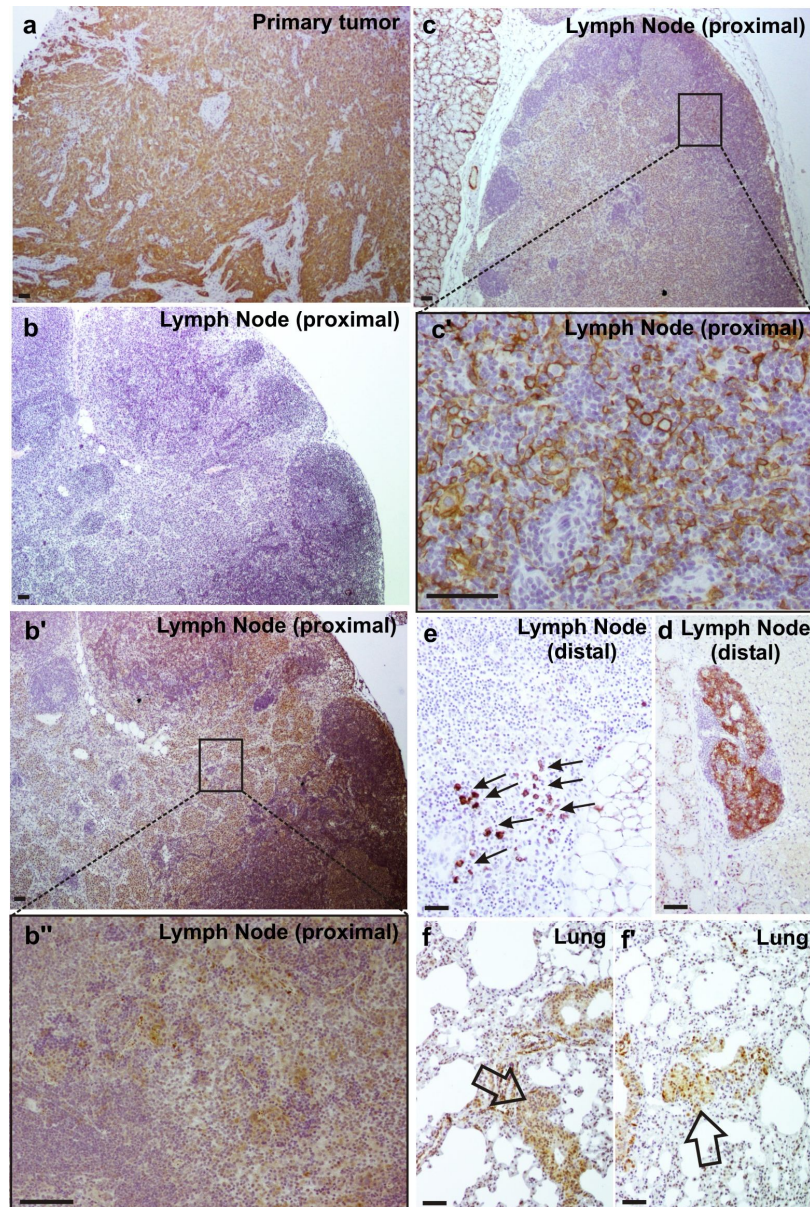


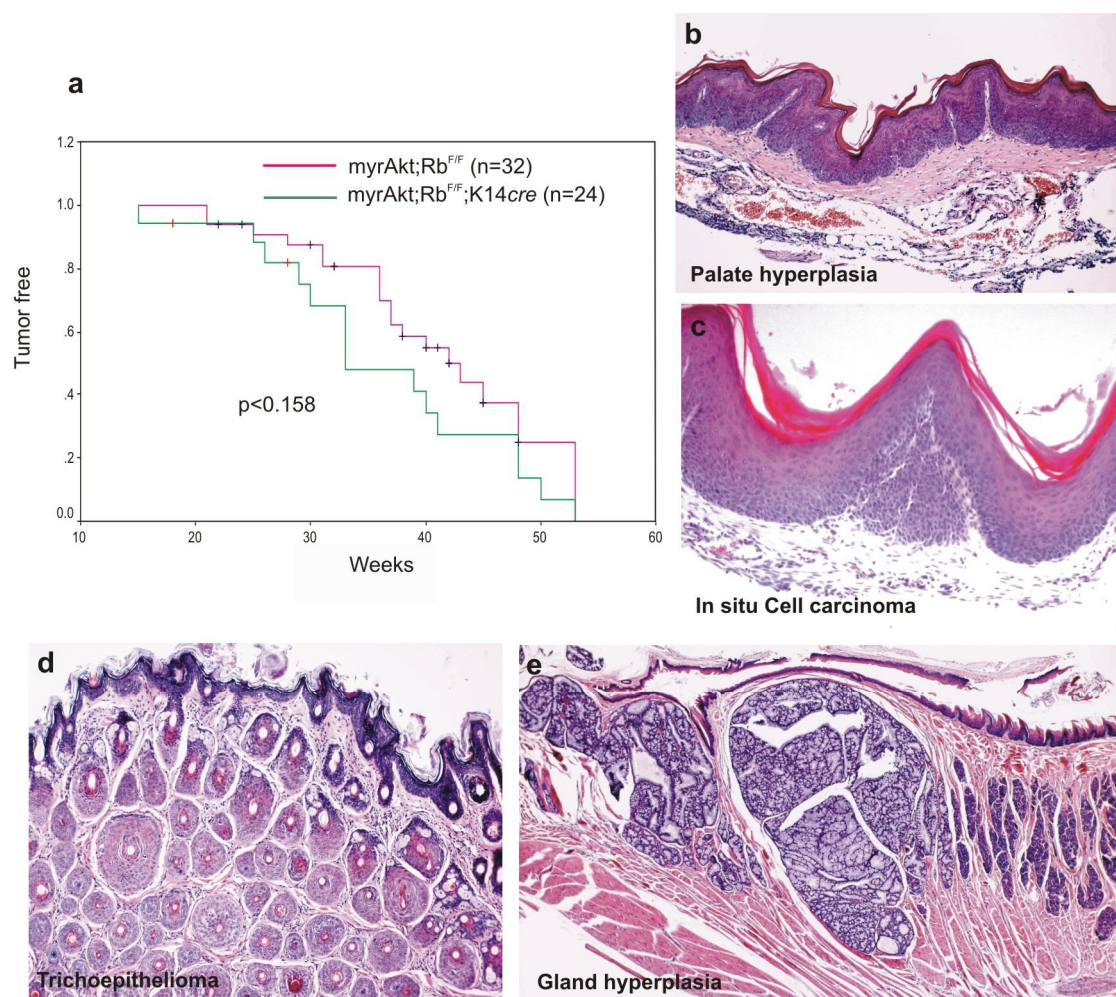
**Supplementary figures**



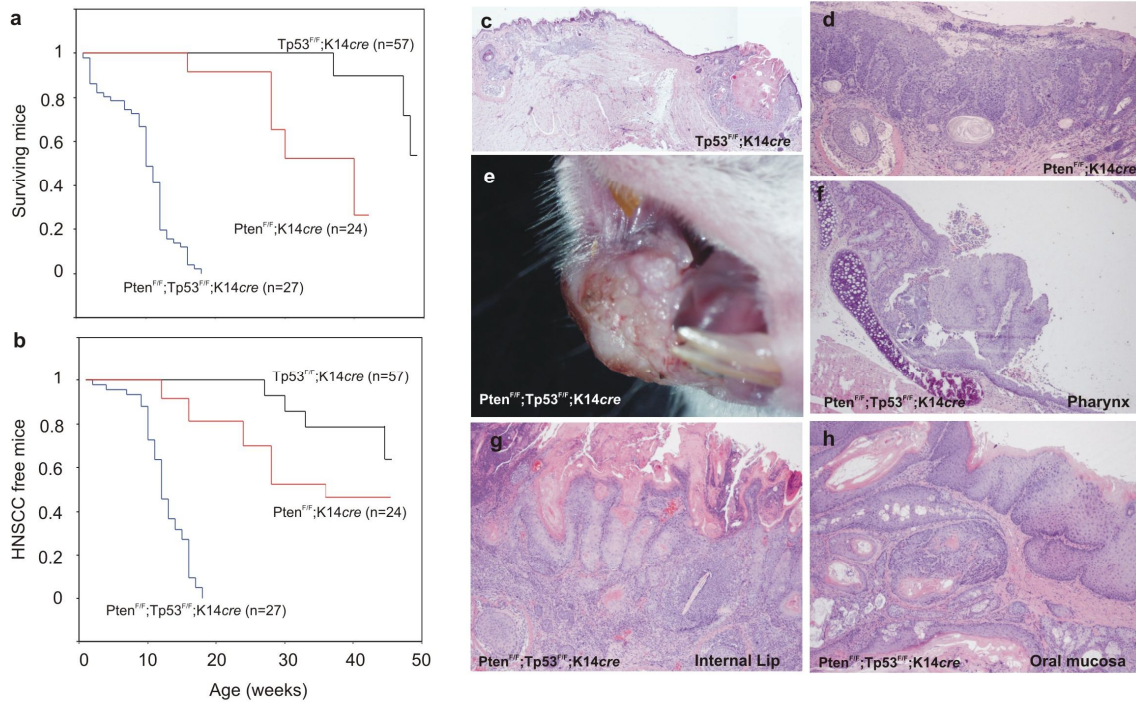
**Supp Fig 1.-** Examples of the expression of phosphorylated Akt (ser473) in oral dysplasia (a) and SCC (b) from myrAkt mice. Hematoxylin-eosin (c, d) and expression of phosphorylated Akt (ser473) (c', d') in human oral dysplasia (c, c') and HNSCC (d, d'). Bars =150  $\mu$ m.



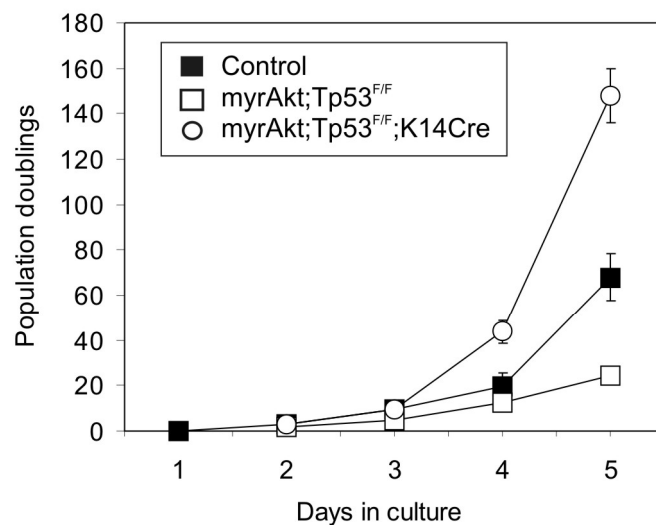
**Supp Fig 2.** Examples of metastatic spreading of oral tumors in *Tp53<sup>F/F</sup>;K14cre;myrAkt* mice. a) Example of primary oral tumor stained with anti K5 antibody. b, b' c) examples of submaxilar lymph nodes showing the infiltration by tumoral cells. b) hematoxylin-eosin staining; b', b'', c' anti Keratin K5 staining. b'' and c'' display higher magnification of the areas denoted in b' and c, respectively. e, d) Examples of tumor infiltrate (denoted by anti keratin K5 staining) in distal (mesenteric) lymph nodes showing spreading of diffuse cells (arrows in e) or massive infiltrate (d). f, f') examples of tumor infiltrate (stained with anti keratin K5) in the lungs (denoted by arrows) of *Tp53<sup>F/F</sup>;K14cre;myrAkt* mice. Bars = 150µm.



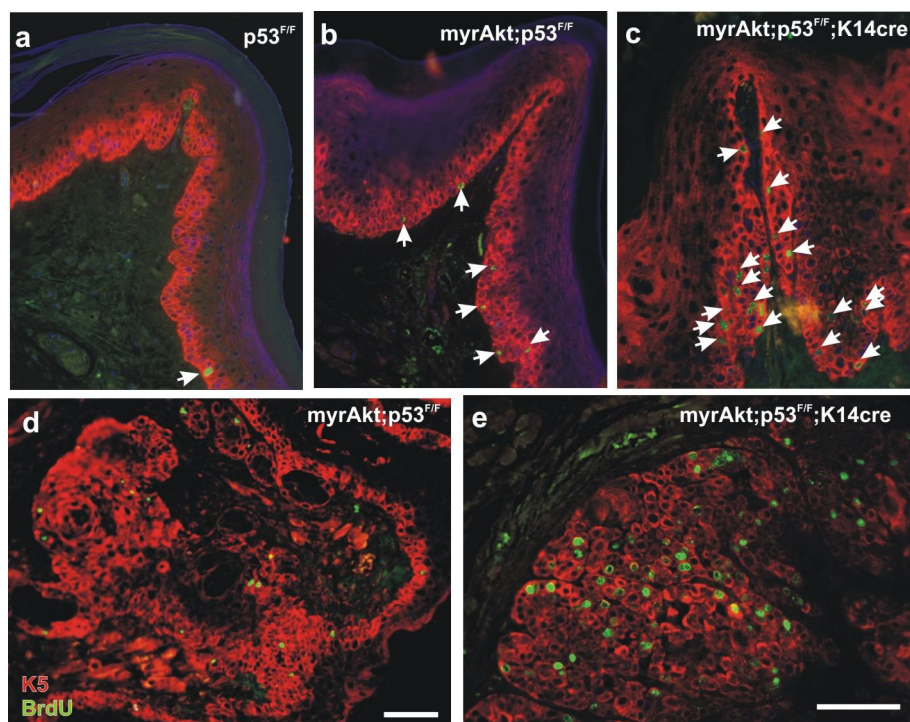
**Supp Fig 3.** a) Kaplan-Meier curves showing the appearance of tumors in mice of the quoted genotypes. b-e) Examples of H&E stained sections of the lesions observed in *Rb<sup>F/F</sup>;K14cre;myrAkt* mice



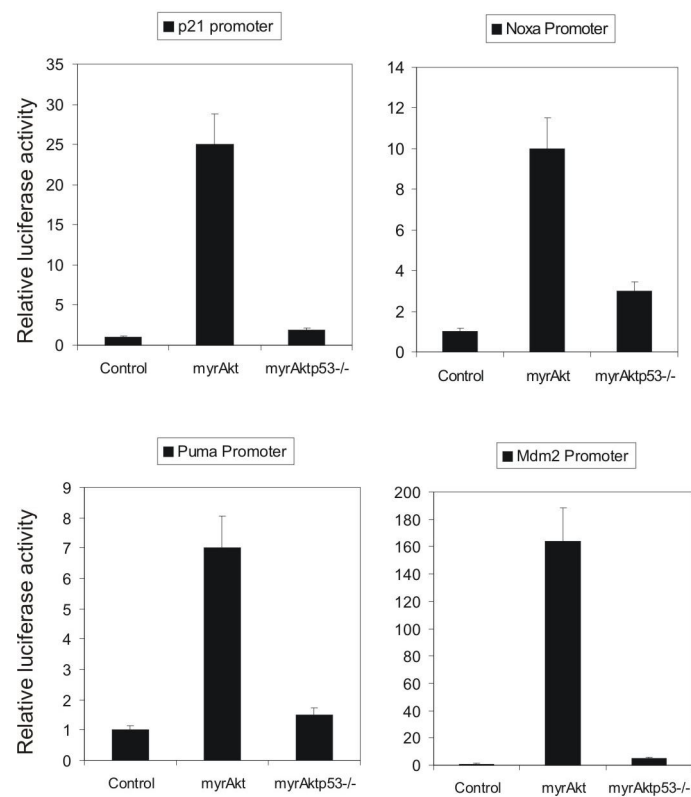
**Supp Fig 4.** a, b) Kaplan-Meier curves showing the survival (a) and the appearance of tumors (b) in mice of the quoted genotypes. c-d) examples of H&E stained sections of the lesions observed in *Tp53<sup>F/F</sup>;K14cre* (c) and *Pten<sup>F/F</sup>;K14cre* (d) mice. e) Gross appearance of oral tumor in a *Pten<sup>F/F</sup>;Tp53<sup>F/F</sup>;K14cre* mouse. f-h) Examples of H&E stained sections of the lesions observed in *Pten<sup>F/F</sup>;Tp53<sup>F/F</sup>;K14cre* mice.



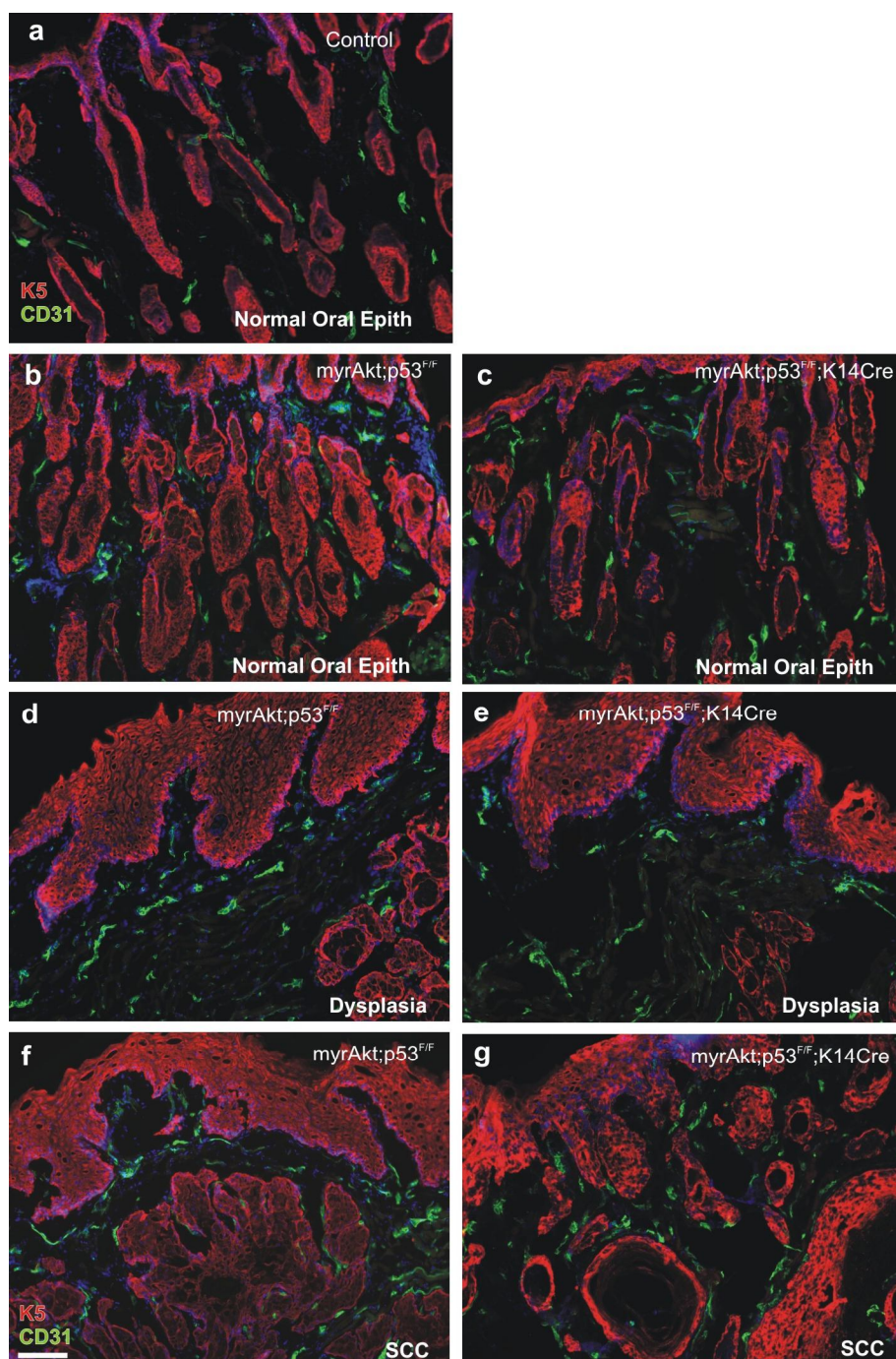
**Supp Fig 5.** Growth curves of primary oral keratinocytes of the quoted genotypes. Note the reduced proliferation of myrAkt cells (myrAkt;Tp53<sup>F/F</sup>), which is radically changed by the subsequent ablation of tp53 tumor suppressor gene (myrAkt;Tp53<sup>F/F</sup>;K14Cre). Data come from three independent experiments and are shown as mean  $\pm$ SD.



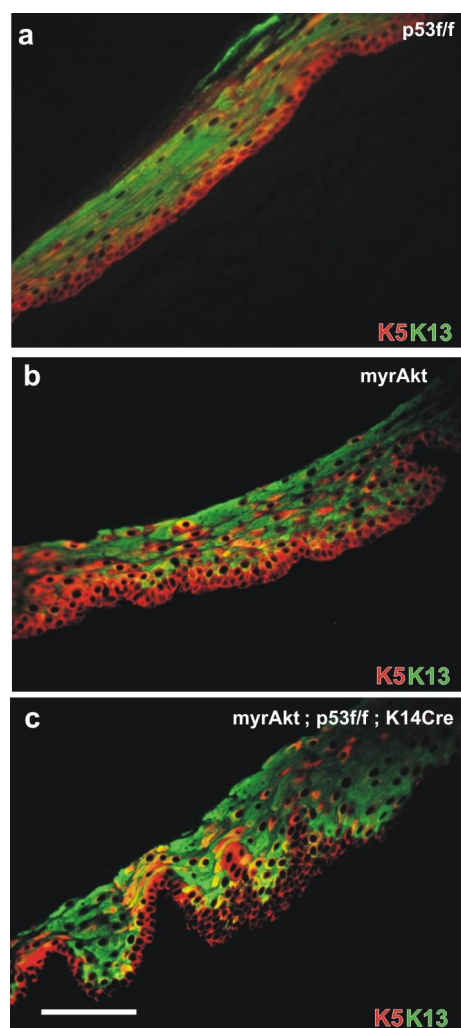
**Supp Fig 6.** Examples of immunofluorescence showing BrdU incorporation in oral tissues and tumors from mice of the quoted genotypes. K5 (red) was used to detect the epithelial component. Arrows denote the BrdU positive cells in non lesional oral tissue. Bars =150 μm.



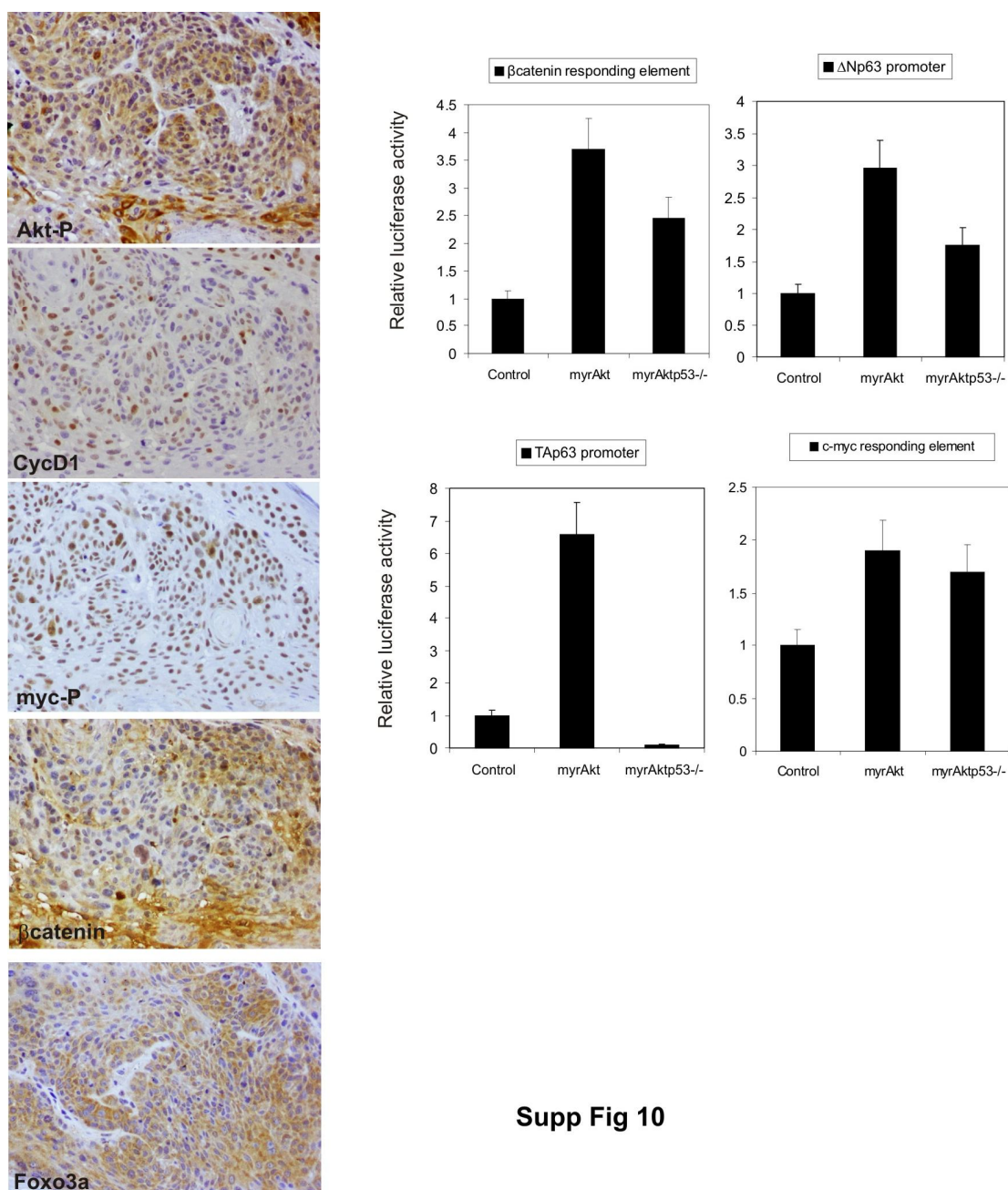
**Supp Fig 7.** Luciferase activity in primary oral keratinocytes from mice of the quoted genotypes upon transfection with the reporter plasmids expressing the specific promoters.



**Supp Fig 8.** Examples of double immunofluorescence showing the presence of blood vessels (stained with CD31-green) in oral tissues and tumors of mice of the quoted genotypes. K5 (red) was used to detect the epithelial component. Bar =150 μm.



**Supp Fig 9.** Differentiation analysis showing K5 (red) and K13 (green) expression in non lesional oral epithelium of mice of the quoted genotype. Bars =100  $\mu$ m.



**Supp Fig 10**

**Supp Fig 10.** Expression of putative Akt targets in oral *Tp53<sup>F/F</sup>;K14cre;myrAkt* mouse tumors previously identified in human HNSCC (Segrelles et al., 2006), and luciferase activity of the quoted reporter plasmids in primary oral keratinocytes derived from mice of the different genotypes.